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Comments presented by People for the Ethical Treatment of Animals
at the December 10-12th 2001 meeting of the
Environmental Protection Agency's
Endocrine Disruptor Methods Validation Subcommittee

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These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and our over 750,000 members and supporters who are deeply concerned about the implications to animals of the Environmental Protection Agency (EPA)'s Endocrine Disruptor Screening Program (EDSP).

Despite the EPA's repeated assurances that it is "strongly committed to animal welfare principles" and to the "development and validation of scientifically sound tests that reduce, refine and replace existing tests,"[1] there has been little evidence of such a commitment in the agency's implementation of the EDSP. For example, it appears as though the non-animal assays being considered for inclusion in the EDSP are limited to ER/AR binding, steroid hormone synthesis, and possibly transcriptional activation. There is no evidence that other available and promising *in vitro* assays have or will be considered for pre-screening or screening purposes in the EDSP.

A case in point is the EPA's treatment of the EDSTAC-recommended high-throughput pre-screening (HTPS) assays. Despite a congressional appropriation of $4 million to develop and validate assays for use in the EDSP, the EPA abandoned these rapid, *in vitro* systems as "unworkable" after only 6 months of research and an expenditure of only $70,000. In contrast, an EPA scientist noted in his presentation to the EDMVS with respect to the proposed Frog Thyroid Assay, that despite notedly high levels of variability with this assay, the EPA was "simply not willing to give up on it." The EPA's bias in favor of animal tests could not be more obvious.

Another example of this bias may be found in a recent e-mail from the same EPA scientist quoted above, in which he asserts that it is "essential to develop and validate whole animal tests before we develop *in vitro* tests. …that to validate the *in vitro* assay, we must first have valid animal test data with which to compare the *in vitro* results. Otherwise we do not know whether or not the *in vitro* assay is relevant to determine the toxicity in the whole animal." We would respectfully remind the EPA that an assessment of relevance, in the context of endocrine assays, relates to the question of whether an animal study is able to accurately assess or predict chemical effects in the species of concern—not inbred rodents. Indeed, the OECD Task Force on Endocrine Disruptor Testing and

[1] Most recently stated by EPA assistant adminstrator, Stephen Johnson in a letter to PETA dated October 30, 2001, as well as in his congressional confirmation hearing.

Assessment (EDTA) has stated very clearly that endocrine assays using rodents and other mammals are intended to assess chemical effects in humans. [2] Given the pitiful predictive accuracy of even such mainstay animal tests as the LD50—which has been found to predict toxicity in humans with at best 65% accuracy[3]—it would be highly inappropriate for the EDMVS to assume that rodent assays will provide an accurate prediction of chemical effects on a biological system as complex as the human endocrine system. This, however, begs the question of how the EDMVS intends to evaluate the relevance of rodent assays to humans. The way in which the EDMVS and EPA choose to address this question will ultimately establish, or destroy, the credibility of the EDSP. What is the value of generating data that are not verifiably relevant to the species of concern? To quote the Environmental Working Group, chemicals would fall into a "bottomless pit of study" in a "regulatory safety zone,"[4] and the public and environment would remain unprotected, which is clearly unacceptable.

Also with respect to validation, there was an obvious lack of clarity among members of the EDMVS regarding the proper criteria by which to judge the "validity" of an assay. Given the admitted lack of experience and expertise on the part of many committee members, and the fact that organizations with tremendous expertise in this regard already exist (i.e., ICCVAM and ECVAM), we call the committee's attention to a recommendation made by the EPA advisory committee that preceded the EDMVS—the former Endocrine Disruptor Standardization and Validation Task Force (SVTF). Just before it was disbanded, the SVTF told the EPA that there was no justification for its proposed bifurcated approach to validating the assays in the EDSP, with the non-animal assays receiving a higher level of scrutiny than the animal-based assays.

The SVTF recommended to the EPA that ICCVAM—which is congressionally mandated to review new and test methods, test methods with new endpoints and test methods with cross-agency application—should be charged with making the final determination of whether or not an assay has been properly validated for regulatory use.

This recommendation was echoed in two unanimous resolutions of the National Toxicology Program (NTP) Advisory Committee on Alternative Toxicological Methods (ACATM), which expressed…

> *…grave concern at the bifurcated approach being taken with review of methods for evaluation of endocrine disruption activity, with ICCVAM considering* in vitro *methods and with the U.S. EPA proposing to review* in vivo *methods using an ICCVAM-like approach. The Committee's primary concern is that both* in vitro *and* in vivo *methods be subjected to the same rigorous peer review and validation process to ensure the highest likelihood of acceptance by the regulatory agencies, the scientific community, and the public.*

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2 Record of the 2nd OECD Expert Consultation on Endocrine Disrupters Testing in Birds (EDB2), November 16-17, 2000.

3 National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). "Multicenter Evaluation of *In Vitro* Cytotoxicity: Summary. September 2000.

4 *BNA Daily Environment Report* 18-Dec-00;243:A-8

> *The ACATM Committee recommends that ICCVAM and the U.S. EPA work together to identify the resources and the related time schedule needed for ICCVAM to evaluate both* in vitro *and* in vivo *endocrine disruptor methods.*
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> *The Committee urges that, with this information in hand, the appropriate senior management consider whether it would be in the best national interest for ICCVAM to evaluate the validation status of both the* in vitro *and* in vivo *methods rather than using the bifurcated approach proposed currently. Resources should be made available from the U.S. EPA, ICCVAM, and other parties as appropriate.* [5]

We again question the EPA's refusal to subject the proposed animal-based assays to the scrutiny of ICCVAM review, as is standard practice for all non-animal assays. Given the fact that the EDSP has broad international implications, involves substantial resources, and will result in important decisions being made, the program begs the use of well-validated methodologies. As stated by members of the NTP ACATM, when activities focus on individual agencies, they tend to be subject to political influences, whereas ICCVAM is apolitical. It represents an efficient, effective, and centralized structure that is already in place and ready to be used.

Moreover, given that the EDMVS is already under tremendous pressure to produce results within a very rigid (and arbitrary) timetable, why is the EPA proposing to re-invent the wheel and add further burden to an already over-taxed committee when it could simply turn to ICCVAM—with its obvious expertise and congressional mandate—to review the final validation status of assays proposed for use in the EDSP? Under this scenario, the EPA or its delegate would be responsible for preparing all detailed review papers (DRP), as well as prevalidation and validation reports for final assessment by ICCVAM, and would reimburse ICCVAM for its services with a portion of the funds appropriated by Congress for the development and implementation of the EDSP. Government advisory committees and members of the public have been posing this question for more than two years now, yet the EPA has never issued a public response or persuasive justification for its proposed bifurcated validation process. We therefore formally request such a response and justification from the EPA.

We have also been told that the assays recommended by the former Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) are "not etched in stone." Why, then, was the EDMVS advised that consideration of structure-activity relationship models (SARs and QSARs) was "beyond the committee's purview," yet several "alternate" or "supplemental" *in vivo* methods and procedures were presented to the EDMVS for consideration. Given that the EDMVS is clearly mandated to "provide independent advice and council…on scientific and technical issues related to validation of EDSP Tier 1 and Tier 2 assays, including reduction of animal use, refining procedures involving animals to make them less stressful and replacing animals where scientifically appropriate," the EPA must grant this committee the flexibility necessary to consider and incorporate new assays and methodologies—particularly *in vitro* and other non-animal systems—into the EDSP in order to reduce the vast number of animals who would otherwise be killed in this program.

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[5] ACATM November 28, 2000 Meeting Summary Minutes.

We also remain concerned that the EPA appears intent on subjecting different assays to differing levels of review. For example, the *in vitro* ER/AR binding/reporter gene assays, which are being validated through ICCVAM, will apparently be subject to the greatest degree of scrutiny, with (1) a detailed review paper, (2) prevalidation report, (3) validation report, (4) integrated summary report, (5) expert consultation, (6) ICCVAM peer review, and (7) EDMVS review of ICCVAM peer review report. In contrast, there was no indication that most animal-based assays would be subjected to expert consultations or external peer reviews. Likewise, EPA representatives indicated that they did not intend to produce a detailed review paper (DRP) for the male and female pubertal assays, the mammalian 2-generation reproductive toxicity study, or the adult 14-day intact male assay, and had even considered providing the EDMVS with only executive summaries of validation studies for review, rather than the complete studies themselves. We are astounded that the EPA would make such a proposal, but are relieved that it was rejected by the EDMVS. However, we remain deeply concerned by comments made by the ICCVAM representative to the EDMVS, that some or all of the DRPs submitted to date are "missing very critical information," including a final standardized protocol and the number and identity of laboratories selected to participate in the prevalidation study. Such omissions would never be tolerated in an ICCVAM review of a non-animal assay, and nor should they be accepted by the EDMVS in its review of animal-based assays.

With respect to individual assays discussed at the meeting, we were distressed to learn that the proposed *In Utero* Through Lactation Assay alone could kill as many as 1,300 animals, which is more than three-times the number who would be killed in all other proposed Tier 1 assays combined. We concur with EDMVS members who concluded that this scale of animal use is unacceptable for a screening assay, and strongly urge the EPA to discontinue any further development of this assay. With respect to the pubertal assays, we were shocked to learn that all research conducted to date has focused exclusively on estrogenic and androgenic effects, without even beginning to consider effects on the thyroid—the very class of hormone it is meant to assess. It is unacceptable that animals have and continue to suffer and die in experiments that have nothing to with the endpoint of interest. Moreover, we strongly object to the cavalier attitude taken by EPA scientists with respect to noted strain differences in the pubertal assays; that "with so many other things to do, the EPA would rather not have to look at strain differences." Such statements reinforce our contention that the EPA would like to "validate" animal-based assays using a rushed and superficial process. Far from being "ICCVAM-like," such a process would be better described as "ICCVAM-***lite***." It is up to the EDMVS to ensure that this does not occur.

Should the EPA fail to properly validate assays intended for use in the EDSP, the agency will be left without the species-relevant data needed to prompt regulatory action for the tangible protection of human health and the environment. In other words, even after millions of animals have suffered and died in crude and cruel chemical poisoning studies, we will be no closer to actually reducing emissions of hazardous chemicals and protecting our environment.

We therefore respectfully request the EDMVS's serious consideration and responsiveness to our comments.